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Metabolic effects of exercise training in hemodialysis patients

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Metabolic effects of exercise training in hemodialysis patients. The effects of 9 ± 6 months of exercise training on lipid and carbohydrate metabolism were studied in six hemodialysis patients. Training lowered triglyceride levels 39 ± 25% ($P < 0.02$) and increased plasma high-density lipoprotein cholesterol levels 23 ± 22% (before, 26 ± 5 mg/dl; after, 31 ± 8 mg/dl; $P < 0.05$). There was a 23% improvement in glucose tolerance ($P < 0.01$) and a 40% reduction in hyperinsulinism ($P < 0.01$) with no significant changes in body weight or diet. There was a 25 ± 8% increase in hematocrits (before, 22 ± 2%; after, 27 ± 2%, $P < 0.01$) and a 29 ± 22% rise in hemoglobin concentrations (before, 7.0 ± 0.8 g/dl; after, 9.0 ± 0.6 g/dl, $P < 0.04$) in five patients. In addition, during training antihypertensive medications could be reduced in three patients with maintenance of normal blood pressure. The improvements in lipid and carbohydrate metabolism diminished when two patients stopped training. These results suggest that physical training can improve some of the metabolic abnormalities observed in hemodialysis patients and could be important as a therapeutic modality.

Effets métaboliques de l'entrainement physique chez les malades en hémodialyse. L'effet de 9 ± 6 mois d'entraînement physique sur le métabolism des lipides et des hydrates de carbone a été étudié chez 6 malades en hémodialyse. L'entraînement a abaissé les concentrations de triglycérides de 39 ± 25% ($P < 0,02$) et augmenté les concentrations de HDL de 23 ± 22% (pré, 26 ± 5 mg/dl; post, 31 ± 8 mg/dl; $P < 0,05$). Il y eu une amélioration de 23% de la tolérance au glucose ($P < 0,01$) et une diminution de 40% de l'hyperinsulinisme ($P < 0,01$) sans modification significative du poids corporel ou du régime. L'hématocrite a augmenté de 25 ± 8% (pré, 22 ± 2%; post, 27 ± 2%; $P < 0,01$) et une augmentation de 29 ± 22% de la concentration d'hémoglobine (pré, 7 ± 0,8 g/dl; post, 9 ± 0,6 g/dl; $P < 0,04$) chez cinq malades. De plus, le traitement antihypertenseur a pu être réduit chez trois malades, la pression artérielle s'est maintenue dans des valeurs normales. Les améliorations des métabolismes des lipides et des hydrates de carbone ont disparu chez deux malades qui ont arrêté leur entraînement. Ces résultats suggèrent que l'entraînement physique peut améliorer certaines anomalies métaboliques observées chez les malades en hémodialyse et peut être une modalité thérapeutique importante.

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Patients with end-stage renal disease who require maintenance hemodialysis frequently exhibit abnormalities in lipid and carbohydrate metabolism [1–4], have hypertension [5], and develop atherosclerosis [6–7]. Many of these metabolic abnormalities accelerate atherosclerosis and its sequellae in hemodialysis patients [6–8]. Exercise training modifies coronary risk factors by improving endocrine-metabolic abnormalities in nonuremic individuals. These include a reduction in plasma triglyceride levels [9–11], an increase in plasma high-density lipoprotein cholesterol concentrations [10, 11], an improvement in carbohydrate tolerance [12–14], and a decrease in high blood pressure levels [15, 16]. This study was designed to determine whether exercise training would have similar beneficial effects on these risk factors for coronary heart disease in hemodialysis patients.

Methods

Patient selection. Six patients requiring hemodialysis for 4 to 6 hours three times weekly to treat end-stage renal disease were studied (Table 1). All provided informed consent. All had anemia and reduced plasma high-density lipoprotein cholesterol levels and received aluminum hydroxide, calcium carbonate, ferrous sulfate, and multivitamins at a stable dose. The men received norandrenalone acetate (100 mg every 2 weeks). Five males had hypertriglyceridemia, and four required drug treatment to control hypertension (Table 1). Two patients (3 and 6) were anephric, and all were oliguric (creatinine clearance of less than 1 ml/min). Patient 1, who smoked cigarettes (20 cigarettes/day) prior to training, discontinued smoking after 7 months of participation.

Table 1. Clinical characteristics of study patients

Patient no.	Age/sex	Diagnosis[a]	Body wt/height *kg/cm*	Duration hemodialysis[b] *months*	Complications[c]	Medication
1	31/M	GN	68.3/183	23	HI, Cardiomegaly Angina pectoris	Propranolol (280 mg/day) Hydralazine (350 mg/day)
2	32/M	GN	149.5/209	48	HT, Cardiomegaly CHF, TX (2)	Prazosin (4 mg/day) Digoxin (0.125 mg/day)
3	26/F	GN	53.2/155	42	Anemia, PTX, TX (2)	—
4	45/M	GN	77.5/180	55	TX (2)	—
5	42/M	HT	95.7/183	23	HT, cardiomegaly	Propranolol (160 mg/day) Hydralazine (400 mg/day)
6	48/M	Cancer	74.1/174	21	HT, cardiomegaly	Clonidine (0.4 mg/day) Prazosin (12 mg/day)
Mean ±SD	37.3 ±8.9			35.3 ±14.8		

[a] GN is glomerulonephritis; HT, hypertension; Cancer, renal cell carcinoma.
[b] Months on hemodialysis prior to exercise training.
[c] HT is hypertension; CHF, congestive heart failure; TX, kidney transplant; PTX, parathyroidectomy.

Patients were selected to participate if: *(a)* they had no medical problems which contraindicated exercise training, such as ventricular arrhythmias, poorly controlled hypertension, or diabetes mellitus with severe retinal disease and/or neovascularization, unstable angina pectoris, hemodynamically significant cardiac valve lesions, congestive heart failure, or severe renal osteodystrophy; *(b)* they were on a stable medication regimen, diet, and dialysis schedule and their interdialysis serum chemistries, blood pressures and hematocrits were stable for at least 6 months prior to study, to guard against the possibility that the changes that occurred during training could be attributed to factors other than exercise; and *(c)* they were motivated to participate. Their primary renal diagnosis was determined clinically or by biopsy, and none had hypothyroidism or diabetes mellitus (Table 1).

Data on a 31-year-old male (173 cm, 57 kg) with insulin-dependent diabetes mellitus of 15 years' duration, who has been exercising on his own for 42 months, are also reported. He has received two unsuccessful renal transplants and has required maintenance hemodialysis for 63 months. His current medications include 14 U of NPH insulin and 8 U of regular insulin in the A.M. and 10 U of NPH in the P.M., calcium carbonate, ferrous sulfate (900 mg/day), and multivitamins. He has been running 2 to 4 miles per day for 27 months.

Experimental design. Initial evaluations included: *(a)* a complete examination by a cardiologist, *(b)* a symptom-limited graded exercise treadmill test according to the protocol of Bruce and Hornsten [17], *(c)* a maximal oxygen consumption test [18], *(d)* two determinations of fasting plasma triglyceride, cholesterol, and high-density lipoprotein cholesterol concentrations and one measurement of fasting lipoprotein lipid concentrations at least 1 month apart, and *(e)* the determination of the plasma insulin and glucose responses to an i.v. glucose tolerance test (20 g). Hematocrit, body weight, and blood pressure were measured routinely at each dialysis, and hemoglobin, blood urea nitrogen, serum creatinine, calcium, phosphate, and albumin were measured monthly. During training, plasma total lipids and high-density lipoprotein cholesterol concentrations were remeasured at 8 week intervals, the cardiovascular evaluation and exercise tests were repeated every 10 weeks, lipoprotein lipid concentrations were remeasured every 12 weeks, and i.v. glucose tolerance tests were repeated every 16 weeks. To control for the degree of uremia and the metabolic effects of heparin, we performed all tests 36 hours after the previous dialysis.

Patients followed their prescribed renal diet during the training program and were instructed to maintain their weight. Food intake was increased keeping diet compositions proportionate, to compensate for the energy expenditure during training to prevent weight loss. Patients were counseled to insure consistency, and careful diet recalls were performed in two patients (1 and 4).

The training protocol was similar to that described for the rehabilitation of ischemic heart disease patients [19] except that initial training intensities were lower and the progression slower due to the reduced exercise capacity in these dialysis

Table 2. Effects of exercise training on lipid metabolism[a]

Patient no.	Duration of exercise *months*	TG *mg/dl*		VLDL-TG *mg/dl*		HDL-TG *mg/dl*		CHOL *mg/dl*		VLDL-CHOL *mg/dl*		LDL-CHOL *mg/dl*		HDL-CHOL *mg/dl*	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	18	279 ±21	194	193 ±52	123	15 ±2	18	200 ±4	175	68 ±15	59	103 ±13	86	24 ±3	34
2	11	457 ±79 174	147 (445)[b]	450 ±4	116 (418)[b]	24 ±11 12	7 (22)[b]	154 ±12	104 (162)[b]	67	24 (88)[b]	68 ±2 91	44 (52)[b]	33 ±3 28	36 (28)[b]
3	11	±16	108 (312)[b]	130	52 (248)[b]	±0.6	15 (20)[b]	139 ±11	149 (191)[b]	27	13 (43)[b]		94 (115)[b]	±3	44 (33)[b]
4	8	1248 ±248	540	1070 ±69	475	19 ±2	15	363 ±35	205	254 ±8	121	72 ±8	62	18 ±2	20
5	3[c]	242 ±84	252	173 ±13	188	13 ±4	8	150 ±6	164	43 ±4	50	70 ±6	87	27 ±2	27
6	3[c, d]	312 ±72	172	167 ±32	86	12 ±5	16	238 ±21	227	58 ±12	49	156 ±38	149	25 ±3	29
Mean ± SD	9.0 ±5.7	452 ±401	236 ±157	364 ±365	173 ±155	16 ±5	13 ±5	207 ±85	171 ±43	86 ±84	53 ±38	93 ±34	87 ±36	26 ±5	31 ±8
P[e]		<0.02		<0.02		NS		NS		NS		NS		<0.05	

[a] Patient numbers correspond to Table 1. "Before" is before training (mean ± SD, 3 determinations), "After" is after training. Abbreviations used are: TG, triglyceride; CHOL, cholesterol; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[b] Five months after cessation of training

[c] Received kidney transplant

[d] Withdrew, nephrectomy

[e] Statistical significance from before training

patients. All training sessions took place in a temperature- and humidity-controlled facility containing a 17 lap per mile track and were supervised by a physician, an exercise physiologist, and an exercise technician trained in cardiopulmonary resuscitation. Emergency medications and equipment, including a defibrillator, were always present and were used once to treat a cardiac arrhythmia.

Initial training began with light calisthenics followed by two 5-min exercise sessions on a bicycle ergometer at a work rate designed to elicit 40% of maximal oxygen consumption. Blood pressure and heart rate and rhythm were monitored during the exercise. At 1 month, depending on each participant's adaptation to the program, rapid walking was added, and alternate periods of walking and jogging were introduced when the patients were able to train at 60% of their maximal oxygen consumption on the bicycle. At 8 months, all patients were walking and jogging up to 2 miles per session and cycling at 65 to 75% of their maximal oxygen consumption. Patients 5 and 6 withdrew from the program for various medical reasons unrelated to conditions of the study (Table 2), but their data are included in the analyses because their work capacity improved during the 3-month period of training. Patients 2 and 3 stopped endurance exercise training on a regular basis after 11 months of participation in the program. After 5 months of no training, their lipids and carbohydrate metabolism were reevaluated.

Analytical methods. Plasma triglyceride, cholesterol, and lipoprotein lipid concentrations were determined by Lipid Research Center techniques [20]. Plasma immunoreactive insulin was measured by the method of Morgan and Lazarow [21] and plasma glucose by the glucose oxidase method (Beckman Instruments, Fullerton, California). Hematocrit, hemoglobin, creatinine, phosphate, calcium, alkaline phosphatase, albumin, and thyroid and liver function were measured by standard autoanalyzer techniques.

The glucose disappearance rates (kg, %/min) were calculated from 10 to 60 min during the i.v. glucose tolerance test by the equation: $kg = 0.693 \div t^{1}/_{2}$, where $t^{1}/_{2}$ is the time it took for glucose to decrease by 50% from its peak value. The insulin area under the curve was computed by trapezoidal integration of the experimental curves from 0 to 120 min after subtracting the basal insulin level. Fasting insulin and glucose levels represent the mean ± SD

of at least three separate determinations on the day of the glucose tolerance test. All data are reported as means ± SD.

Statistical methods. Data were analyzed by the paired *t* test and the signed Rank test [22].

Results

Exercise testing. Initially, the graded exercise treadmill test duration for these six dialysis patients was shorter (332 ± 105 sec) and their mean maximal oxygen consumption lower (18.1 ± 3.7 ml O_2/kg/min) than that commonly found in healthy sedentary people of the same age and sex ($P < 0.001$) [23, 24]. After 9 ± 6 months of training, the graded exercise treadmill test duration had increased 41% ($P < 0.02$; Fig. 1) and there was an increase in the maximal oxygen consumption of everyone except patient 4 (22 ± 21%, $P < 0.10$, $N = 6$, Fig. 1). The maximal oxygen consumption and graded exercise treadmill test duration of the patient who has been training on his own for 42 months were 34.5 ml O_2/kg/min and 580 sec, respectively. The maximal oxygen consumption of patient 2 decreased by 12% after 5 months without training. Patient 3 did not return for retesting.

Lipid and carbohydrate metabolism. Training was associated with a 39.2 ± 24.8% reduction in fasting plasma triglyceride levels ($P < 0.02$, Table 2), a 44.3 ± 28.8% reduction in very-low-density lipoprotein triglyceride concentrations ($P < 0.02$, Table 2) and a 23.0 ± 21.7% increase in plasma high-density lipoprotein cholesterol levels ($P < 0.05$, Table 2). Patient 5 gained 3 kg during training and did not demonstrate any of these changes. The changes in both plasma triglyceride and high-density lipoprotein cholesterol levels were gradual and maintained over the training period in the four patients who trained for longer than 3 months (Fig. 2, A and B). The changes in the plasma concentrations of the other lipoprotein classes during training were variable, and not statistically significant (Table 2). The cessation of exercise in patients 2 and 3 was associated with a decrease in their plasma high-density lipoprotein cholesterol levels and a rise in the triglyceride and cholesterol concentrations of the other lipoprotein classes (Table 2).

Prior to training, all patients had normal fasting plasma glucose levels and a normal glucose disappearance rate (Table 3). In the five patients who were retested, there was a 6.3 ± 2.4% reduction in fasting plasma glucose concentrations ($P < 0.01$) and a 22.5 ± 7.3% improvement in glucose disappearance rates ($P < 0.01$, Table 3). Fasting plasma insulin levels were high in these patients prior to training and decreased 40.1 ± 16.4% in the patients retested after training ($P < 0.01$, Table 3). Exercise training also resulted in a 38.0 ± 21.8% reduction in the integrated insulin areas calculated above the fasting insulin levels during the i.v. glucose tolerance test ($P < 0.02$, Table 3). In patients 2 and 3, a cessation in training was associated with a decrease in their glucose disappearance rates and an increase in their insulin levels (Table 3).

There were no significant changes in these six patients' body weights (change, −0.13 ± 1.8 kg) or percent body fat (before, 17.8 ± 8.6%; after, 17.8 ± 7.1%) during training. The weight of the participants varied by less than ±3 kg during the program and did not correlate with the lipid changes. After the cessation of regular training, patient 2 gained 4

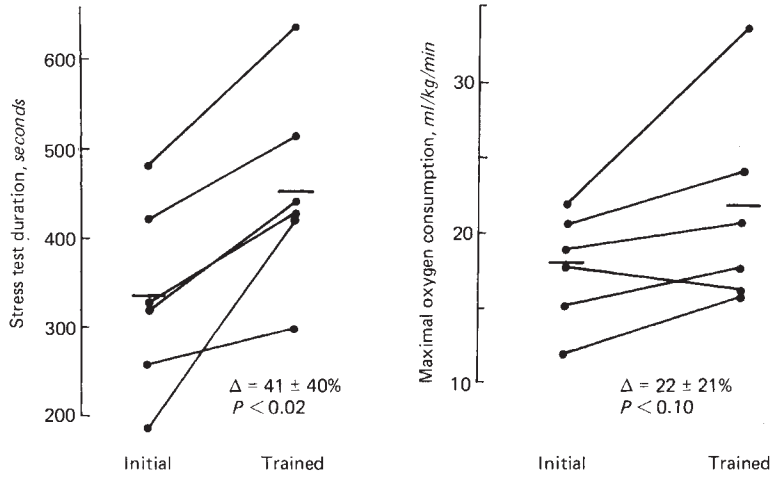

Fig. 1. *Graded exercise treadmill stress test duration and maximal oxygen consumption before and after training.*

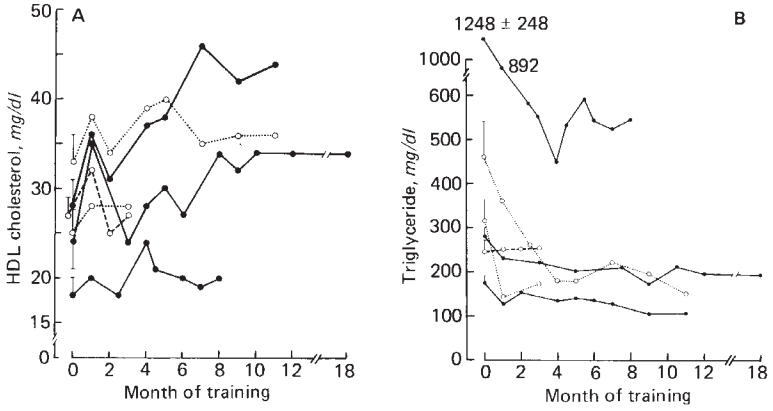

Fig. 2. *Sequential effect of exercise training on* **A** *plasma triglyceride levels and* **B** *plasma HDL cholesterol levels.*

kg, and patient 3 maintained a stable weight. Dietary recalls revealed a 13% increase in total calories in patient 1 over a 15-month period of training and a 9% increase in calories in patient 4 over 6 months, with small changes in the composition of both their diets. In patient 1, the percentage of calories from protein was 17% initially, 16% at 6 months, and 14% at 15 months; fat represented 36% initially, 37% at 6 months, and 41% at 15 months; and carbohydrate was 48%, 47%, and 45% of the calories, respectively. In patient 4, the pretraining calorie distribution was 18% as protein, 35% as fat, and 47% as carbohydrate; after 6 months it was 19% protein, 33% fat, and 48% carbohydrate.

Hypertension. The antihypertensive medications of three of the four hypertensive patients were reduced in dosage or discontinued during the training program because of a decrease in blood pressure. A normal blood pressure was maintained despite the following reductions in medicines. *Patient 1:* Hydralazine was discontinued, propranolol reduced by 220 mg/day. *Patient 5:* Hydralazine was reduced 100 mg/day, clonidine reduced 0.2 mg/day. *Patient 6:* Prazosin was discontinued, clonidine reduced 0.2 mg/day. When patient 1 reduced his training effort for 2.5 months, his blood pressure rose and antihypertensive medication had to be reinstituted; a return to a regular training schedule reduced his blood pressure and permitted a reduction in the dosages of his antihypertensive medication. Exercise training also appeared to lower the blood pressure of the patient who trained on his own for 3 years. When he began dialysis therapy in 1974, he required α-methyldopa (2 g/day), hydralazine (100 mg/day), and propranolol (80 mg/day) for control of blood pressure. With the maintenance of a regular exer-

Table 3. Effects of exercise training on glucose metabolism[a]

	Fasting plasma glucose *mg/dl*		Glucose disappearance rate, *%/min*		Fasting plasma insulin *μM/ml*		Integrated insulin area *μU/ml/min*	
Patient	Before	After	Before	After	Before	After	Before	After
1	88	83	1.71	2.12	24	11	3510	2820
2	108	99	0.79	0.89	88	37	3155	1036
		(100)[b]		(0.82)[b]		(80)[b]		(1860)[b]
3	86	80	1.31	1.73	23	17	4480	2750
		(80)[b]		(1.61)[b]		(19)[b]		(2885)[b]
4	88	81	1.69	2.12	27	15	4080	2070
5	87	—	0.76	—	16	—	3680	—
6	82	80	1.57	1.86	14	11	2200	1890
Mean	90	85	1.31	1.74	32	18	3518	2113
± SD	±9	±8	±0.44	±0.51	±28	±11	±792	±728
P[c]	<0.01		<0.01		<0.01		<0.02	

[a] "Before" is before training; "After," after training.
[b] Five months after cessation of training
[c] Statistical significance from pretraining level

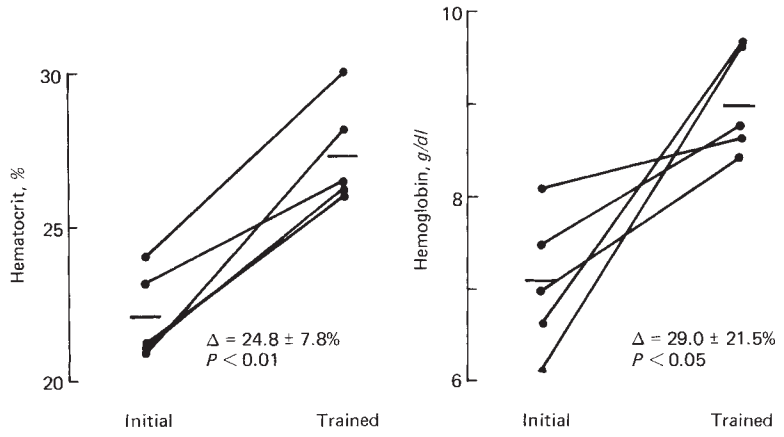

Fig. 3. *Effect of exercise training on hematocrit and hemoglobin levels in five male dialysis patients.*

cise program, his blood pressure has been in the normal range for the last 12 months on 60 mg/day of propranolol.

Anemia. All patients had low hematocrits (21.7 ± 1.7%, $N = 6$) and hemoglobins (6.9 ± 0.8 g/dl, $N = 6$) that varied by less than 2.0% for the 6 months prior to training. The data on the effects of training on anemia in the female patient were uninterpretable because she had regular menses and required transfusions of 2 or 3 U per month. Therefore, they are not included. In the five male patients who trained for at least 3 months, there was a rise of 24.8 ± 7.8% in hematocrits (before, 22.1 ± 1.5%; after, 27.4 ± 1.7%; $P < 0.01$, Fig. 3) and 29.0 ± 21.5% in hemoglobin concentrations (before, 7.1 ± 0.8 g/dl, after, 9.0 ± 0.6 g/dl; $P < 0.04$; Fig. 3) during training, with no change in their dose of ferrous sulfate or norandrenalone acetate. Their reticulocyte counts and serum albumin concentrations were also unchanged. There was also a rise in the hematocrit of the patient who has been training on his own for 42 months. His hematocrit was 25% prior to training and rose to 45% after 9 months of training. He now runs 2 to 4 miles per day and maintains a hematocrit of 42%, despite discontinuation of norandrenalone acetate after 12 months of training.

Discussion

Results in this study demonstrate that some hemodialysis patients have a very low work capacity and that a moderate endurance training program can improve both their exercise tolerance and some of their endocrine-metabolic abnormalities. The mean maximal oxygen consumption of dialysis patients in this study was lower than that of age- and sex-matched sedentary normal controls, patients with ischemic heart disease [25], or patients with a chronic illness, such as diabetes mellitus [13, 14]. It was also lower than that reported by Lundin et al [26], in a somewhat younger group of dialysis patients. The reduced graded exercise treadmill test duration found in our dialysis patients is consistent with their low maximal oxygen consumption. Training resulted in a gradual improvement in both of these tests, but levels still remained well below the normal range. Despite the rather small increase in maximal oxygen consumption, exercise training was associated with improvements in glucose metabolism and some parameters of lipid metabolism, a reduction in hyperinsulinemia, a rise in hematocrit, and an attenuation of hypertension in some of these patients. It is possible that other cointerventions, such as changes in diet, body weight, cigarette smoking, or other health-related habits, could have occurred in these patients and influenced their metabolism to some extent. But these were monitored, and remained relatively constant. Furthermore, the metabolic changes that occurred in the individual who stopped smoking were comparable to the effects in other patients.

Exercise training was associated with a significant increase in plasma high-density lipoprotein cholesterol concentrations in the five patients in whom plasma triglyceride levels decreased. In the two patients who stopped training, plasma triglyceride levels increased, and high-density lipoprotein concentrations decreased to levels comparable to those observed prior to participation in the program. The mechanism by which increased physical activity lowers triglyceride and raises the plasma level of high density lipoprotein cholesterol in nonuremic man is thought to be mediated by an exercise-induced increase in the activity of lipoprotein lipase [27]. Because the lipid abnormalities in

dialysis patients are due to a reduction in the activity of this enzyme [28, 29], it is possible that these lipid changes reflect an increase in the level of lipoprotein lipase activity.

The elevation in plasma insulin may contribute to the lipid disorder observed in dialysis patients by promoting the synthesis and production of triglyceride-rich lipoproteins by the liver [1, 2, 30]. Physical training improves insulin sensitivity and glucose metabolism in normal individuals and adult onset diabetics [11–13, 31], and results in this study indicate that it will improve glucose metabolism and reduce insulin resistance in hemodialysis patients. If there is a reduction in the frequency and intensity of training, however, these improvements diminish. The magnitude of the changes in lipid and carbohydrate metabolism that occurred during training was greater than would have been anticipated due to changes in diet or body weight. It is also unlikely that major changes in body composition occurred, because body weights and percent body fats remained constant in these patients. Although changes in the dose of antihypertensive medications could have contributed to the improvement in lipid and carbohydrate metabolism observed in patients 1 and 6, these metabolic improvements also occurred in the three patients (2, 3, and 4) whose medications were not changed during training. Furthermore, the return of plasma lipid levels, glucose disappearance, and hyperinsulinemia toward pretraining levels in the patients who stopped training suggests that the training effect was primary.

There was a reduction in the blood pressure of three of the four hypertensive patients during the training program, which permitted a reduction in dosages of peripheral vasodilator types of antihypertensive medications. This suggests that exercise may lower blood pressure in some dialysis patients by reducing peripheral vascular resistance, but exercise-induced changes in sodium-volume homeostasis, the renin-angiotensin system, and the sympathetic nervous system might also play a role [32, 33]. There was also an increase in hematocrits and hemoglobin concentrations of all the male dialysis patients during training. These increases could be due to hemoconcentration or changes in doses of antihypertensive medications, rather than an exercise-induced increase in red cell mass [34]. Hematocrit levels increased, however, in two patients (2 and 4) whose medications were not altered during training. These increases in hematocrit and hemoglobin seemed to be greater than would have been expected due to changes in plasma volume alone, because there were no significant changes in serum albumin concentrations or postural hypotension to suggest significant hemoconcentration. Determinations of red cell mass and plasma volume are critical for the resolution of these questions. Nevertheless, even if the changes in blood pressure and/or hematocrit levels are due to a reduction in the extracellular fluid volume, they would be of clinical benefit to dialysis patients whose fluid volume and blood pressure are frequently difficult to control.

This study presents preliminary evidence that exercise training has the potential to ameliorate some of the endocrine-metabolic abnormalities and coronary risk factors in dialysis patients. Before training programs can be initiated on a larger scale, further investigation will be required to determine the optimal training program for dialysis patients of different ages and disabilities, and to fully understand the physiologic responses of these patients to training.

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